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S Larkin

Mayo Clinic School of Medicine, Rochester

Elizabeth K. Blixit

CentraCare Health

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Lipoid proteinosis: Unfamiliar skin findings delay diagnosis



Sydney Larkin, BA,^a Elizabeth K. Blixt, MD,^b Neeraj Kumar, MD,^c
Robert E. Watson, Jr, MD, PhD,^d Nneka I. Comfere, MD,^{e,f} and Jennifer L. Hand, MD^{e,g,h}
Rochester and St Cloud, Minnesota

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INTRODUCTION

Lipoid proteinosis (LP) is a rare, inherited condition that progresses gradually with multisystemic manifestations. Histopathologic characteristics can be understated, delaying the diagnosis if a high degree of suspicion is not present.

REPORT OF CASE

A 21-year-old Somalian man presented with uncomfortable skin fragility and thickening that was progressive since childhood. He described recurrent asymptomatic blisters on his extremities that ruptured and healed with scarring, reduced mobility of his hands and feet caused by thickened palmoplantar skin, and painful thickening of his tongue and lips. Family history included parental consanguinity (first cousins) and a similarly affected sister. On examination, he appeared older than his stated age and spoke with a soft, hoarse, breathy voice. He had generalized, diffuse wrinkling and nummular, atrophic, 6-mm to 2-cm patches over his shoulders, axillae, left flank, hands, and groin (Fig 1). His mucosal lips and tongue were enlarged with a rugated, papillomatous texture (Fig 1). A 5-year seizure history prompted neurologic evaluation. Magnetic resonance imaging (MRI) found low-signal foci centered in the amygdalae (Fig 2).

Histopathologic assessment of lesional skin in the axilla, referred without clinical impression for LP, was initially interpreted as nondiagnostic. Verhoeff Van Gieson stain highlighted slightly diminished, fragmented elastic tissue fibers in the superficial dermis. With evidence of distinctive neuroimaging findings, there was clinical suspicion of LP. Review of

Abbreviations used:

CT:	computed tomography
ECM1:	extracellular matrix protein 1
LP:	lipoid proteinosis
MRI:	magnetic resonance imaging

skin biopsies found eosinophilic hyaline deposits surrounding eccrine glandular structures. Periodic Acid-Schiff diastase and type IV collagen immunohistochemical stains highlighted eosinophilic hyaline material (Fig 3). Cutaneous, neurologic, radiologic, and otolaryngologic findings clinically confirmed the diagnosis of LP. Genetic consultation and testing of peripheral blood found confirmatory homozygous mutations [c.580T>G; p.Phe194Val.] in the extracellular matrix protein 1 (*ECM1*) gene. To treat this patient's mouth discomfort and reduced hand mobility, oral acitretin was initiated. After a daily dose of 25 mg (0.35 mg/kg) for 12 weeks, he showed softening of his hands and feet with increased flexibility and mobility and described decreased soreness of his mouth and tongue.

DISCUSSION

LP is due to an *ECM1* gene mutation that results in deposition of hyaline material in the skin, mucous membranes, and internal organs. Dermatologic manifestations such as yellow, beaded papules at the eyelid margin (moniliform blepharosis), are often subtle. Generalized skin thickening most commonly affects the face and extremities.¹ In areas of mechanical friction, blisters and scars can form from even

From the Mayo Clinic School of Medicine^a; CentraCare Clinic, St. Cloud^b; the Departments of Neurology,^c Radiology,^d Dermatology,^e Clinical Genomics,^g and Pediatrics and Adolescent Medicine^h; and Division of Anatomic Pathology,^f Mayo Clinic.

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Correspondence to: Jennifer L. Hand, MD, Department of Dermatology, Mayo Clinic, 200 First St SW, Rochester, MN 55905. E-mail: hand.jennifer@mayo.edu.

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Fig 1. Signs of LP on physical examination. **A**, Atrophic patches on shoulder (*arrows*) and fine wrinkling. **B**, Diffuse thickening of the tongue causing scalloped borders and papillomatous texture.

minor trauma. A hoarse voice is typically the first and most prominent clinical sign.² Calcification of the amygdalae can lead to epilepsy and neuropsychiatric abnormalities. Characteristic calcification is evident on MRI and is confirmed on computed tomography (CT).³ These findings prompted further consideration of the LP diagnosis in our patient (Fig 2).

On histopathologic evaluation, LP is characterized by progressive eosinophilic hyaline material along the dermoepidermal junction, blood vessels, and adnexal structures, making it difficult to distinguish from more diffuse dermal diseases.⁴⁻⁶ The distinction between lipoid proteinosis and cutaneous amyloid deposition is challenging in the early stages, as hyaline eosinophilic deposits may stain with thioflavin T and weakly with Congo red in both disorders. Further diagnosis of LP is clarified by periodic acid–Schiff–positive and diastase-resistant staining of hyaline deposits and ultrastructural

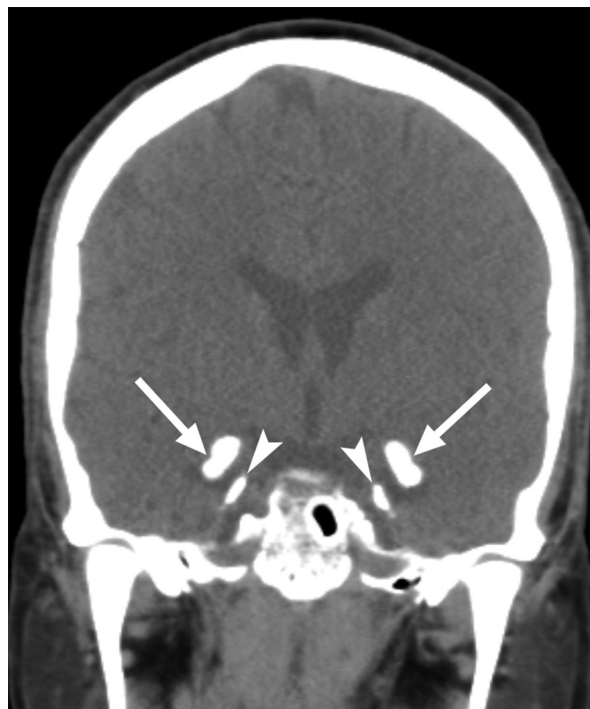


Fig 2. Neuroimaging. Follow-up CT confirmed that the low signal foci on the MRI showed typical bright CT appearance of calcifications (*arrow*). Also, CT accentuated some smaller bilaterally symmetric calcifications at the adjacent parahippocampal gyri (*arrowheads*). This unique imaging appearance is very suggestive of LP.

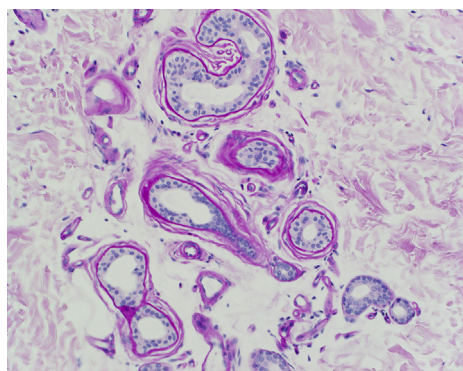


Fig 3. Skin histopathology. Peri-ecrine eosinophilic, hyaline-like deposition is accentuated with periodic acid–Schiff diastase reaction. (Original magnification: $\times 200$.)

examination finding of concentric rings of basement membrane material, reduplication of the lamina densa at the dermoepidermal junction, and dermal fibroblasts revealing cytoplasmic vacuole formation.⁶ Direct immunofluorescence studies using antibodies to type IV and type VII collagen antibody highlight thick bands at the dermoepidermal junction and around blood vessels that suggest hyaline basement membrane thickening. These stains are

not histologically diagnostic but rather supportive for lipoid proteinosis.⁶

Treatment of LP is difficult with little information available. Retinoids are found to modulate the metabolism of type IV collagen synthesis, inhibit the proliferation of fibroblasts and type III collagen, and decrease hyaline material and deposited collagen in the dermis.⁷ Our patient had an excellent response to acitretin, which highlights a potential role for retinoids in the treatment of cutaneous and mucosal LP.

This case illustrates the diagnostic challenge of LP. Cutaneous findings were subtle and nonspecific and histopathologic features not readily apparent. Communication of clinical suspicion for LP when skin biopsy specimens are submitted for pathologic review is important to ensure proper identification of these potentially subtle, typical histopathologic features. Collaboration with providers in multiple specialties is necessary to establish this diagnosis.

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